UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/335,689	06/18/99	TOUSIGNANT J	6969.0028

HM12/0725

FINNEGAN HENDERSON FARABOW
GARRETT & DUNNER LLP
1300 I STREET NW
WASHINGTON DC 20005-3315

EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
1632	8

DATE MAILED: 07/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary	Application No. 09/335,689	Applicant(s) Tousignant
	Examiner Richard Schnizer	Group Art Unit 1632

☒ Responsive to communication(s) filed on *May 22, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-30* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-30* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4,5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Applicant's election with traverse of the species of linear and cyclical RGD sequences in Paper No. 7 is acknowledged. The traversal is on the ground(s) that examination of the other nine claimed species would not be a serious burden. These nine species include such diverse compounds as antibodies, lectins, undefined "agents to target the LDL receptor", lactose, and a variety of peptides. Clearly the breadth of the claimed species constitutes a burdensome search. Accordingly, the requirement is still deemed proper and is therefore made FINAL.

Claim Objections

Claim 16 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 16 is drawn to a micellar complex according to claim 9. Further limitations regarding the characteristics of a group of micellar complexes are recited, but groups of micelles are not claimed. No further limitations on individual complexes are set forth, therefore the claimed complexes are indistinguishable from those of claim 9.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention comprises methods of making micellar complexes wherein the size distribution of the resulting complexes is "substantially homogenous" and may vary by less than 20% relative to the average size of the complexes in the group. The invention also comprises the compositions made by the method, and methods of using the compositions. As set forth below in the rejections under 35 U.S.C. 112, second paragraph, the definition and scope of "substantially homogenous" are unclear, however it is apparent that a size variation of less than 20% from the mean is within the scope of the invention. Thus, for the purpose of examination under 35 U.S.C. 112, first paragraph, all claims are considered to encompass a population of micelles in which the size distribution varies by less than 20% relative to the mean size of the complexes in the group.

The prior art discloses methods which produce groups of complexes with a much broader range of absolute size variation than that of the instant invention. See Figs. 2-4. However, in no case does Applicant disclose the production of a group of micellar complexes which vary in size by less than 20% from the average size in the group. For example, in Fig. 3C Applicant produces complexes ranging in diameter from 0 to about 100 nm, with an apparent average of about 30-40 nm. Thus the range of variation exceeds 100%. In Fig. 4 Applicant discloses several compositions having an average diameter of about 100 nm which appear to vary over a range of 50-100%. Finally, at page 39 of the specification, Applicant discloses that the preferred size range of particles is 25-250 nm, a 10-fold variation, whereas that obtained by the prior art is 200-800 nm, only a 4-fold variation. This suggests that the percent variation of the prior art method may be less than that of the claimed method. Applicant provides no teaching or example of how to use the claimed method to produce a group of complexes wherein the size distribution of the resulting complexes varies by less than 20% relative to the average size of the complexes in the group. Thus one of skill in the art would have to perform undue experimentation in order to do use the claimed methods as intended, or to make or use the claimed compositions.

In further consideration of claims 6, 13, and 21, the invention comprises a method of coating the micellar complexes of the invention with a "hydrophobic species". The invention also comprises the resulting composition and a method of using it.

The specification discloses that the "hydrophobic species" are lipids or other compositions used in the pharmaceutical arts to coat compositions and formulations. The only guidance in

terms of actually executing the claimed method is on page 20 of the specification wherein it is disclosed that the coating process may consist of mixing the hydrophobic species with the micellar complex. The specification provides no examples or guidance as to how one would successfully coat a micellar complex and avoid simple integration of the hydrophobic species into the micelle. Further, as discussed below in rejections under 35 U.S.C 102, the simple addition of a hydrophobic species to the micellar compositions appears to be indistinguishable from the method of formation of the micellar compounds. That is, in the method of making the micelles, lipids are added to DNA which condenses around the positively charged head groups of the lipids. Lipids which do not immediately interact with the DNA would ostensibly be available to coat the micellar complexes. Applicant has not taught how to avoid this process in favor of some distinct coating process, and one of skill in the art would have to perform undue experimentation in order to develop a coating technique in the absence of any guidance or examples in the specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 25-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-16 are indefinite for several reasons. First, the meaning of "substantially homogenous micellar lipids" is unclear. The specification does not distinguish between substantial and insubstantial homogeneity, thus a skilled artisan is not apprised of the metes and bounds of the claimed invention. Second, it is unclear what is intended to be homogenous about the lipids. Are the lipids homogenous in composition, size, molecular weight, length of acyl chains, or any or all of the above? Third, the term "micellar lipids" is confusing because, while the combination of cationic lipids with a PEG derivative might result in the formation of lipid micelles, it is unclear how this could result in the production of lipids of any kind, unless an undisclosed chemical reaction is intended. Fourth, the claims require "a sufficient amount of PEG". It is unclear what amount is sufficient because the purpose for which the PEG is required is unknown. This purpose appears to be the production of substantially homogenous group of lipid micelles, however the specification fails to adequately define what constitutes such a group. Finally, the claims require the combination of a cationic lipid with a PEG derivative "in an amount suitable to produce" micellar lipids. It is unclear to what the phrase "amount suitable" applies. Does it apply to both the cationic lipid and the PEG derivative, or to just one or the other, or perhaps to a volume of liquid in which the two are combined?

Claim 4 is indefinite because it depends from itself. Claim 4 has been examined as if it depended from claim 1.

Claims 4 and 15 are indefinite because they recite a 1:8 ratio of lipids to DNA, but recite no units by which to measure each substance. Those of skill in the art frequently express such

ratios in terms of moles of lipid per unit mass of DNA, or in terms of the charges of the two molecules. On what characteristic of each substance should one rely to calculate the ratio in order to meet limitations of the claim?

Claims 16 and 25-30 are indefinite because a single claimed complex is described in terms of the size distribution of a group of complexes. The size distribution of a group of complexes is not a characteristic of a single complex, and cannot be used logically to describe a single complex.

Claims 25-30 recite the phrase "a substantially homogenous size distribution". This phrase is indefinite because the specification does not provide a limiting definition. At page 17, an example is given wherein the size distribution of a traditional lipid complex may vary by greater than 50%, whereas that of the instant invention may vary by only about 20%. Is "about 20%" variation intended to be the definition of "substantially homogenous"? What is encompassed by "about 20%"? Would a size distribution varying by 25-30% infringe on the invention? The claims are indefinite because the meaning of "substantially homogenous" cannot be determined from the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3, 6, 9-11, 13, 14, 16-19, 21, 22, 24-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Harris et al (US Patent 5,719,131, issued 2/17/98).

Harris teaches a method of making micellar complexes comprising a cationic lipid, a PEG derivatized colipid, and DNA. See column 26, lines 4-11 and 32-36; column 37, lines 24-53; and column 45, line 56 to column 46, line 5. It is noted that, for the purposes of examination under 35 U.S.C. 102, the claims were not considered to encompass a population of micelles in which the size distribution varies by less than 20% relative to the mean size of the complexes in the group, unless this limitation was explicitly recited in the claim. Claims 6, 13, and 21 are included in this rejection because these methods and compositions do not appear to be distinguishable from the teachings of Harris. Specifically, the claims are drawn to micellar compositions coated with a hydrophobic species. The specification teaches that the compositions are made by adding the hydrophobic species to the micellar compositions. This would seem to be inherent in the method of making the initial micellar compositions. The addition of lipid micelles to DNA would result in condensation of the DNA around cationic lipids, and any uncomplexed lipids would be available to coat the DNA. In light of the description of the invention in the specification at page 20, it would seem that hydrophobic coating of the micelles would be unavoidable.

Thus Harris anticipates the claims.

Claims 1-3, 6-14, 16-19, and 21-30 rejected under 35 U.S.C. 102(e) as being anticipated by Unger (US Patent 6,028,066, filed 5/2/97).

Unger teaches a method of making micellar complexes by combining micellar lipids with a bioactive agent which may be DNA. See column 79, lines 20-37; column 2, lines 59-65; column 6, lines 10-24, especially lines 22 and 23; and column 6, lines 55-57. The micellar lipids may comprise PEG-modified lipids. See column 22, line 19 to column 24, line 1, especially column 22, lines 60-67. The complexes may comprise targeting moieties, and may include peptides with RGD sequences. See column 6, lines 45-51; and column 19, lines 54-58. Unger also teaches delivery of the complexes to mammalian airway cells. See column 84, lines 24-28.

It is noted that, for the purposes of examination under 35 U.S.C. 102, the claims were not considered to encompass a population of micelles in which the size distribution varies by less than 20% relative to the mean size of the complexes in the group, unless this limitation was explicitly recited in the claim. Claims 6, 13, and 21 are included in this rejection because these methods and compositions do not appear to be distinguishable from the teachings of Harris. Specifically, the claims are drawn to micellar compositions coated with a hydrophobic species. The specification teaches that the compositions are made by adding the hydrophobic species to the micellar compositions. This would seem to be inherent in the method of making the initial micellar compositions. The addition of lipid micelles to DNA would result in condensation of the DNA around cationic lipids, and any uncomplexed lipids would be available to coat the DNA. In light

of the description of the invention in the specification at page 20, it would seem that hydrophobic coating of the micelles would be unavoidable.

Thus Unger anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 15, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris et al (US Patent 5,719,131, issued 2/17/98).

Harris teaches a method of making micellar complexes wherein a cationic lipid and DNA are present in 64 different ratios including 0.7:1, 1.4:1, 5.6:1, and 11.2:1. Harris does not teach the lipid to DNA ratio of 8:1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine cationic lipid and DNA in a ration of 8:1. One would have been motivated to do so because the concentration of each of these components is a result-effective variable. That is, the results of a technique using the composition are effected by concentrations of each of these variables, and one of ordinary skill would be motivated to optimize the concentrations of each variable. Generally, differences in concentration will not support the patentability of subject

matter encompassed by the prior art unless there is evidence indicating that this concentration is critical. See MPEP 2144.05(b). In this case, the specification and claims disclose that ratios of 1:1 and 8:1 will yield the claimed compositions. See Figures 3 and 4, and claims 4, 15, and 20. Thus the claimed ratio of 8:1 does not appear to be absolutely required for the function of the invention. Harris teaches ratios covering the range of ratios disclosed as functional by Applicant. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re 0Aller*, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955).

Thus the invention was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton, can be reached at 703-308-2801. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Richard Schnizer, Ph. D.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER